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Final Technical Report
A Spectroscopy of Helix Melting
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Progress Report

1. Publications which have appeared since last renewal.

1. Normal Mode Calculation for Methylated Z-DNA poly(dG- m^5dC) · (dG - m^5dC), (with X. Hua). Biopolymers **27**, 645-655 (1988).
2. Solitons hiding in DNA and their possible significance in RNA transcription. Phys. Rev. **A38**, 1538-1541 (1988).
3. Hydrogen bond melting in B-DNA copolymers in a mean field self-consistent phonon approach (with V.V. Prabhu and L. Young). Phys. Rev. **B39**, 5436-5443 (1989).
4. Calculation of far-infrared absorption in polymer DNA, (with L. Young and V.V. Prabhu). Phys. Rev. **A39**, 3173-3180 (1989).
5. Vibrational Free Energy, Entropy and Temperature Factors of DNA Calculated by a Helix Lattice Approach, (with K.S. Girirajan and L. Young). Biopolymers, **28**, 1841-1860 (1989).
6. Helical Lattice Vibrational Modes in DNA (with V.V. Prabhu, W.K. Schroll, and L.L. VanZandt) Phys. Rev. Lett. **60**, 1587 (1988).

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7. Phonon Interpretation of Inelastic Neutron Scattering in DNA Crystals (with W.K. Schroll, V.V. Prabhu and L.L. Van Zandt). *Biopolymers* **28**, 1189-1193 (1989).
8. Prediction of a fluctuational local mode in B-form poly(dA)·poly(dT) (with K.M. Awati) *Phys. Rev. A* **40**, 497-500, (1989).
9. Breathing modes near a junction of DNA double helices (with Y. Feng, R.D. Beger, X. Hua) *Phys. Rev. A* **40**, 4612-4619 (1989).
10. Calculated effect of propeller twist in a DNA: its absorption in the far-infrared region (with L. Young, V.V. Prabhu) *Phys. Rev. A* **40**, 5451-5454 (1989).
11. Localized fluctuational hydrogen-bond stretch modes in homopolymer DNA (with K.M. Awati) *Phys. Rev. A* **40**, 6521-6530 (1989).
12. Nonlinear model of the DNA Molecule (with M. Techera and L.L. Daemen) *Phys. Rev. A* **40**, 6636-6642 (1989).
13. Vibrational fluctuations of hydrogen bonds in a DNA double helix with nonuniform base pairs (with Y. Feng) *Biophys. J.* **57**, 547-553 (1990).
14. Defect-mediated hydrogen-bond melting in B-DNA polymers (with V.V. Prabhu, L. Young, K.W. Awati, and W. Zhuang) *Phys. Rev. B* **41**, 7839-7845 (1990).
15. Analysis of the breakdown of continuum and semidiscrete approximation of a nonlinear model for the DNA double helix (with Mario Techera and L.L. Daemen) *Phys. Rev. A* **41**, 4543-4546 (1990).

16. Dependence of defect-mediated hydrogen-bond melting in the DNA double helix on the size of an induced defect (with W. Zhuang). Phys. Rev. **A41**, 5677=5682 (1990).
17. Prediction of modes with dominant base roll and propeller twist in B-DNA poly(dA)·poly(dT) (with L. Young, V.V. Prabhu and G. Edwards). Phys. Rev. **A41**, 7020-7023 (1990).
18. Selfconsistent calculations of localized DNA vibrational properties at a double-helix single-strand junction with anharmonic potential (with W. Zhuang). Phys. Rev. **A41**, 7033-7042 (1990).
19. Analysis of a nonlinear model for the DNA double helix: Energy transfer in an inhomogeneous chain (with M. Techera and L.L. Daemen). Phys. Rev. **A42**, 1008-1011 (1990).
20. Vibrational fluctuations of hydrogen bonds in a DNA double helix with alternating TA type inserts (with R. Beger and Y. Feng). J. Biophys. **58**, 437-445 (1990).
21. Comments on DNA Solitons with realistic parameters (with M. Techera and L.L. Daemen). Phys. Rev. **A42**, 5033-5035 (1990).
22. Observation of preferred direction melting in a lattice model of DNA-poly(dA·dC)·(dG·dT) (with V.V. Prabhu and L. Young). Biopolymers **31**, 355-358 (1991).
23. Criterion of thermal denaturation for modified-self-consistent-phonon-theory mean-field calculations in DNA polymers (with Y.Z. Chen and Y. Feng) Phys. Rev. **B42**, 11335-11338 (1990).

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24. Calculation of temperature dependence of interbase breathing motion of a GC double helix with AT inserts (with Y. Feng and W. Zhuang), *Phys. Rev. A* **43**, 1049-1053 (1991).
25. Criterion of DNA melting in the mean-field MSPA theory (with Y. Feng). *Phys. Rev. B* **43**, 9284-9286 (1991).
26. A self-consistent mean-field calculation of a homopolymer DNA strand separation: Bond breaking in a macromolecule (with Y.Z. Chen), *J. Chem. Phys.* **94**, 4665-4667 (1991).
27. Premelting thermal fluctuational base pair opening probability of Poly(dA)·poly(dT) as predicted by MSPA (with Y.Z. Chen and Y. Feng) *Biopolymers* **31**, 139-148 (1991).
28. Method for calculating the effect of a rigid enzyme on the dynamics of a large DNA helix (with R. Beger). *Phys. Rev. A* **43**, 5672-5677 (1991).
29. Method for calculating the effects of a dynamic entity interacting with poly(dT-dA)·poly(dT-dA): A dynamic enhancer-repressor action (with R. Beger). *Phys. Rev. A* **44**, 3997-4004 (1991).

Survey of recent progress

We will survey the progress over the last two years briefly to conserve space. The overriding theoretical problem in DNA calculations is twofold. Firstly, the size of the molecule is large and even the size of the smallest repeat unit, the homopolymer unit cell, is of dimensionality of 123 by 123. Biologically significant units are many times this size. The second factor

is that one must deal with the nonlinearity of the system. A most important biophysics problem is the dynamics of strand separation. The complete breakdown of a bond is necessarily a nonlinear effect. Methods are available to calculate nonlinear behavior but because of the calculational complexity they require simple systems. The harmonic approximation handles large interacting systems but it is difficult to incorporate nonlinear effects. Our approach has been basically a two pronged approach. We analyze the full nonlinear problem in a simple model for DNA and we do the full dimensional calculation in the harmonic approximation where the nonlinear behavior is approximated by MSPA adjustments to the nonlinear elements.

We analyze a simple model of DNA in papers 2, 12, 19, and 21 with explicit calculations of the nonlinear behavior of the hydrogen bonds. We found that approximate solitary waves could propagate in homopolymer or uniform repeating polymers. When we introduced more random base sequences, the scattering destroyed the propagation. These waves were only possible at low amplitudes $\approx 0.05A$ stretch for the h-bonds. The energy carrying capacity was limited.

We found an additional feature which dominated the large amplitude large energy regime. Large amplitude excitations became trapped or localized even in homopolymer DNA. The nonlinearities caused softening in the region of large amplitude motion which then stayed put for long periods of time, at least several hundred picoseconds. this localization was also studied by MSPA methods and its significance will be discussed in more detail later.

The nonlinear calculations did reproduce effects seen in our MSPA calculations, i.e., softening of the h-bond vibrational motion characterized by a frequency drop, and large nonlinear increase in fluctuation or squared am-

plitude with increasing temperature. The nonlinear and MSPA calculations differ in too many details for exact comparison but the general agreement in behavior was encouraging. Many papers here deal with technical details of such calculations.

The other prong of the melting work is the MSPA incorporation of nonlinear effects into normal mode calculations. This effort can be broken down into four distinct areas of effort. They are 1) the mean field uniform repeat DNA calculations. 2) The defected calculation which emulates a system where the melting grows from an initiation or nucleation site. This is the more realistic calculation as one expects melting to grow from a nucleation site. 3) Unique sequence melting. 4) Localized fluctuations that may cause an instantaneous open state fluctuation that may close or serve as the nucleation site for type 2 calculations.

For the mean field work in papers 3, 24 and 25 we extended the earlier simple calculations to more base sequence cases and found that the predicted critical temperatures do scale with observed melting temperatures. All mean field temperatures are high compared to the expected true melting temperature as mean field melting is an upper limit to physical melting. The later works attempted more accurate calculations of melting behavior. The principle result is that one can't sensibly improve the agreement with experiment. This led to a realization of the limitations of the approach as currently developed. The Morse potential is appropriate to bonds dissociating in vacuum rather than dissolving in a fluid. In the later case, the base atoms, originally bonded, form new h-bonds to solvent water molecules. More exact calculations don't show the sharp transition associated with such a transition without modification of the potential and some modification of the method-

ology. The clearest example of this is actually shown in paper 27. This work calculates the fluctuational single base pair opening probability in the premelted region as a function of temperature. The agreement with experimental observation is excellent up to within 10K of the melting temperature. At closer to the melting temperature the increase in opening probability is too small as the probability must approach one half at the melting temperature. The potential across the h-bonds has to involve more chemistry. We have to assume that the h-bond stretch is the proper reaction coordinate for change from simple h-bonding to water h-bonding. The fluctuation then is the mechanism for crossing the saddle point in this reaction coordinate. The motion however that causes the crossing of the saddle point is still the collective motion of the double helix. That is the same D parameter we have been using. We find a great sharpening of melting behavior for such a modified potential. Further work on this will be discussed later. We find that even without this modified potential the MSPA does show nonphysical (melted) behavior.

The defected calculations that allow melting from a nucleation site papers 4, 16 and 22 still show abrupt loss of self consistent solution which gives a sharp criterion for melting behavior that is in excellent agreement with observed melting temperatures. We also studied a range of sizes of initial defect and show that the melting temperature doesn't depend on the initial details of the defect. Paper 22 finds that the melting is directional where such directionality is not ruled out by symmetry. For the information content of DNA to have sense such directionality is necessary.

The unique sequence melting, topic three is an attempt to study the melting behavior of those regions in DNA where processes such as transcription

begin. There are highly conserved sequences such as TATAAT that seem to be open state nucleation sites. The calculations aim at understanding the dynamics of the opening at such sites when they are embedded in a long section of helix. Only two such works have been completed to the point of melting, paper 18. A number of other unique sequences have been analyzed but without the calculation yet extended to melting temperatures. This is described in papers 9, 13 and 20. These and several other cases are being studied currently for melting behavior. The solution at room temperature is a necessary first step.

The fourth class of MSPA calculations deals with the ability of excitations which can break bonds to appear as fluctuations. Vibrations are bosons and have large fluctuations. The nonlinear nature of the h-bond excitations greatly enhance the ability to achieve large fluctuations. The problem is closely related to the self trapping localization found in our simple model nonlinear calculations discussed earlier. When done in the full dimensionality these fluctuations become highly probable and are localized by the nonlinear trapping to a single base pair. The localization is very sharp. We predict that these excitations would likely absorb energy in a broad band about 60 cm^{-1} in poly(dA)·poly(dT). A large absorption is seen at these frequencies by Edwards et al. in this polymer. These excitations can be the source of the nucleation sites needed for our defect melting assumptions. The logical loop can be closed by the incorporation of these fluctuations. The work is described in papers 8 and 11. Paper 25 carries out the statistics and predicts the probability of base pair opening which is in better agreement with observation than other approaches.

Other work has gone on in addition to the work related to melting. We

have worked at improving our basic parameters and to improve our agreement with experimental observations. We have calculated the compressional acoustic velocity and compared the results to inelastic neutron scattering data. This work is in papers 6 and 7. We have explored what is needed to fit far-infrared absorption data. Good spectra has recently become available from the group at the Max Planck in Stuttgart. The refinement to this data is in papers 4,10 and 17. Vibrational temperature factors were calculated in paper 5 to compare to the width of lines in x-ray structure analysis. The effects of methylation on i.r. spectra was studied in paper 1. Overall our models fit the available experimental data very well. Recently Weidlich et al. and Edwards et al. have substantiated an early prediction of ours. They have found that all polymer DNA have a mode near 85cm^{-1} regardless of base sequence. Also Powell has verified that for much of the spectra single strands have most modes quite similar to duplex strands as predicted by our early calculations.

Paper 28 is the first work of a new area we are entering. Most DNA dynamics is limited to DNA in the absence of interaction with the enzymes that are known to be present in biological process. We believe that to some extent we can explore the effects of certain models of enzymes on the dynamics of the DNA. This will relate more to the actual biologically significant dynamics. These enzymes are typically of the size of several times 10^5 atoms. They interact typically with 70 base pairs or several $\times 10^4$ DNA atoms. The dynamics of importance will have long time scales as much mass movement is involved. The combined size and time scale make it unlikely that the problem will be tractable by standard MD simulations.

In our unique sequence work we have developed methods of cutting and

splicing different dynamical systems to create new systems. By our Green function methods we find the dynamics of the new systems based on prior solutions of the old systems. It is possible to carry out such an analysis even when relatively little is known of one of the initial elements. The Green function needs a limited amount of information in one system to allow us to calculate effects in the better known system. For example if one knew or assumed a density of states for the less known system, and postulated a set of forces and motions at the points of connection between this system and well known system, one could calculate detailed effects on the better known system.

In paper 28 "Toward a method for calculating the effect of enzyme on the dynamics of the DNA double helix" we analyze the effect of simple mass loading of an enzyme on the h-bond stretch motion of the helix. The effects are considerable. The hydrogen stretch motion shifts down in frequency to about half its previous value. The fluctuation level experiences, an accompanying rise in magnitude. We believe that careful spectroscopy may detect such shifts in spectra in mixed DNA enzyme systems if done carefully. We believe that the spectrum of the enzyme itself may be inferred from careful spectroscopy and used to improve the calculations.